

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

NOVARTIS PHARMACEUTICALS)
CORPORATION, NOVARTIS AG,)
NOVARTIS PHARMA AG, NOVARTIS)
INTERNATIONAL PHARMACEUTICAL)
LTD. and LTS LOHMANN THERAPIE-)
SYSTEMEAG,)

Plaintiffs,)

v.)

NOVEN PHARMACEUTICALS, INC.,)

Defendant.)
_____)

C. A. Nos. 13-00527 & 14-111 (RGA)

(Consolidated)

NOVEN'S REPLY POST TRIAL BRIEF ON INVALIDITY

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I. INTRODUCTION

Defendant Noven Pharmaceuticals, Inc. (“Noven”) respectfully submits this Reply Post-Trial Brief, responding to Plaintiffs’ Responsive Post-Trial Brief on Validity (D.I. 168) (“Pl. Br.”).¹

Noven has shown by clear and convincing evidence that claims 7 and 16 of the ’031 patent are invalid for obviousness by presenting evidence that at the time of the alleged invention, a POSA would have maintained a reasonable expectation that rivastigmine was particularly susceptible to oxidative degradation, coupled with the prior art’s undisputed disclosure of transdermal devices containing rivastigmine and the use of antioxidants to prevent oxidative degradation in pharmaceutical formulations. By avoiding the scientific basis for the POSA’s expectation of rivastigmine’s susceptibility, and choosing to challenge Noven’s obviousness defense with collateral evidence designed to distract from the teachings of the prior art, Plaintiffs have done nothing to diminish the clear and convincing evidence so presented.

II. OBSERVING RIVASTIGMINE’S OXIDATIVE DEGRADATION IS NOT A PATENTABLE INVENTION

Plaintiffs’ cases do not stand for the proposition that a patentable invention lies, *per se*, in the discovery or observation of a problem itself. (Pl. Br. at 2.) Rather, the obviousness inquiry must consider whether the POSA would have reasonably expected the problem or what the prior art as a whole would have suggested to the POSA. *See, e.g., Chapman v. Casner*, 315 F. App’x. 294, 298-299 (Fed. Cir. 2009) (Rader, Cir. J., dissenting, noting that evidence of whether a POSA would have expected a problem is part of the obviousness analysis); *In re Peehs*, 612 F.2d 1287, 1290 (C.C.P.A. 1980) (determinative question for obviousness was whether cause of problem would have been recognized by POSA); *In re Nomiya*, 509 F.2d 566, 571-72 (C.C.P.A.

¹ All citations are to the docket in C.A. No. 13-527-RGA unless otherwise noted.

1975) (obviousness inquiry hinged on whether the prior art suggested the existence of the problem solved).

Leo Pharm. Prods. v. Rea, 726 F.3d 1346 (Fed. Cir. 2013) is not on point. In that case, claims to the combination of a Vitamin D analog, corticosteroid and a particular solvent were found nonobvious. The prior art's failure to recognize the stability issue, however, was attributed to its consistent teaching away from mixing Vitamin D analogs with other drugs in the first place, rendering the POSA without motivation to combine the Vitamin D analog and corticosteroid, and thus unable to have observed the compatibility. *Id.* at 1353-54; 55, 57. Further, the court found that the eventual solution (use of a particular solvent) was not even known, or among a finite set of possible solutions, and it was not predictable. *Id.* at 1356-57. Finally, the court found the most probative evidence of nonobviousness was secondary considerations in the form of unexpected results, commercial success, and that the invention satisfied a long-felt but unsolved need. *Id.* at 1358-59. *See also Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, 581 F. App'x. 859, 864 (Fed. Cir. 2014) (distinguishing *Leo Pharm. Prods.*).

In the present case, the prior art is not alleged to "teach away" from the use of an antioxidant with rivastigmine. The use of an antioxidant is a well-known predictable solution to resolving oxidative degradation, and there is no evidence of secondary considerations supporting the nonobviousness of the claimed subject matter.

The *Omeprazole* case, 536 F.3d 1361 (Fed Cir. 2008), is likewise distinguished. Claims to a pharmaceutical preparation containing an omeprazole core, an inert subcoating on the core, and an enteric outer-layer were found nonobvious because the prior art was deemed to have expressly endorsed an enteric-coated tablet without a subcoating, thus providing no motivation to

the artisan to contemplate the addition of one. *Id.* at 1380. The court also noted that the prior art contained other solutions to the stability issue that the POSA would have tried before that of the invention, making the invention not even obvious to try. *Id.* at 1380-81.

In the present case, the prior art does not present an express endorsement of rivastigmine transdermal patches without an antioxidant, especially since GB '040 (JTX 19) contains only disclosure of an unfinished, unmarketable formulation. (SOF 33.)² And, unlike *Omeprazole*, the use of antioxidant is a common solution to address oxidative degradation in pharmaceutical formulations. (SOF 85, 95-98, 183-85, 200; SOF Response 423, 427-28, 431.) Furthermore, the prior art in the present case instructed the POSA to consider the structural features of the pharmaceutical compound that could give rise to degradative issues, and the evidence presented by Dr. Schöneich demonstrates that the POSA would have identified features in the rivastigmine molecule rendering it “particularly susceptible” to oxidative degradation (a conclusion reinforced by the POSA’s awareness of nicotine and its known propensity to oxidize). (SOF 111, 133, 142-150, 157-59, 161-165; SOF Response 244, 396, 416, 429.) As such, the POSA would not have been surprised to observe oxidative degradation (Tr. at 81:1-6)³ and would have employed the well-known solution of antioxidant use.

The *Merck* case does not support Plaintiffs’ position either. *Merck & Co., Inc. v. Sandoz, Inc.*, No. 10-16252012 WL 266412 (D.N.J. Jan. 30, 2012). In *Merck*, the invention of an acetate-buffered formulation of a drug (employing acetate outside of its normal buffering range) was deemed nonobvious because the challenger introduced no evidence that the POSA had knowledge of the drug’s degradation issue and that the claimed solution was even known or that

² Citations to “SOF” are to the numbered paragraphs of the statement of facts included with Noven’s Opening Brief (D.I.162). Citations to “SOF Response” are to the numbered paragraphs of Noven’s Responses to Plaintiffs’ counter statement of fact, appended hereto.

³ Citations to “Tr.” are to D.I. 154-156 in C.A. No. 13-527.

a POSA would have had a reasonable expectation of success in the claimed solution. *Id.* at *4, *8-10. The court noted that the evidence confirmed the only path to a solution was through trial and error, with no prior art pointing to the ultimate solution. *Id.* at *8.

In contrast, evidence has been presented in this case that a POSA would have had a reasonable expectation of rivastigmine's susceptibility to oxidative degradation and that use of an antioxidant was a predictable solution selected from a small, finite group of such solutions. (SOF 155, 157-160, 166, 183-185, 430; SOF Response 252, 280, 363, 420, 427-28, 439.) In such cases, like those distinguished in *Merck*, the claimed invention is actually "obvious to try" and thus obvious. *Id.* at *3-4.

III. A POSA WOULD HAVE REASONABLY EXPECTED RIVASTIGMINE TO OXIDATIVELY DEGRADE BASED ON ITS CHEMICAL STRUCTURE

A POSA would have expected rivastigmine to be particularly susceptible to oxidative degradation from an examination of its chemical structure during preformulation. Upon examination of the structure, a POSA would have immediately recognized the presence of three structural features in rivastigmine that render a specific carbon-hydrogen bond in the molecule "particularly susceptible" to oxidation: the carbon-hydrogen bond is *immediately adjacent* to each of (i) an aromatic ring (*i.e.*, the carbon-hydrogen bond is at a benzylic position); (ii) a tertiary amine; and (iii) an additional carbon substituent ($-\text{CH}_3$), making the carbon a tertiary carbon. (SOF 158-60.) Dr. Schöneich explained that a POSA would have understood that each of these features, by stabilizing the resulting radical at that carbon, cause this particular carbon-hydrogen bond in rivastigmine to be weak and therefore particularly susceptible to oxidation. (SOF 143-45, 159.) Dr. Klivanov never contested these basic principles or their application to rivastigmine.

A. Dr. Schöneich's Opinions Are Not "Theoretical"

Dr. Schöneich's opinions that a POSA would immediately recognize from an examination of the structure that rivastigmine has a weak carbon-hydrogen bond are not "theoretical" as Plaintiffs argue, but rather are based on well-known chemical principles that determine if a particular bond in a molecule will be weak and therefore susceptible to oxidation. (SOF 142-150; Noven Br. at 4-6.) Indeed, Carey and Sundberg confirms that a POSA would know, consistent with Dr. Schöneich's testimony, that benzylic and tertiary positions (the subject position in rivastigmine is both) are "especially susceptible" to oxidation:

Substrates that are relatively electron-rich or that provide particularly stable radicals are the most easily oxidized. *Benzylic*, allylic, and *tertiary positions are especially susceptible to oxidation*.

(DTX 32 at 693, emphasis added; SOF Response 361.) Moreover, Dr. Schöneich explained how the tertiary amine, which is immediately adjacent to the benzylic/tertiary position in rivastigmine further weakens the carbon-hydrogen bond at that position by stabilizing the resulting radical. (SOF 147, 158; SOF Response 447.) This effect is also undisputed by Dr. Klibanov.

B. Testing Would Not Have Been Required for a POSA to Determine that Rivastigmine Is Particularly Susceptible to Oxidation

Testing would not have been required for a POSA to determine that rivastigmine is particularly susceptible to oxidative degradation under pharmaceutically relevant conditions. Plaintiffs' statement that "a POSA would have first needed to conduct tests to recognize the stability problem solved by the '031 patent" is incorrect and is not "undisputed" as Plaintiffs contend (Pl. Br. at 12). To the contrary, Dr. Schöneich testified that a POSA would have examined the structure of rivastigmine during preformulation development and would have "*immediately recognized* based on organic chemistry knowledge" the structural features that make rivastigmine "particularly susceptible" to oxidation. (Tr. 48:2-49:13, emphasis added.)

What is undisputed is that testing is necessary to determine to what extent, if any, oxidation occurs in a particular formulation *after* the problem is identified. After the susceptibility is identified, a POSA would not have been surprised when they actually observed the expected degradation. (Tr. 81:1-6.)

The prior art cited by Plaintiffs' expert confirms that a POSA would not have required testing to identify a stability problem. *Modern Pharmaceuticals*, for example, explains that it was routine practice for a POSA to apply "functional group chemistry" in order to identify "the potential modes of degradation that drugs molecules will likely undergo." (PTX 153 at 181; SOF 111, 133; SOF Response 366.) Indeed, examination of the chemical structure was a "fundamental step" in preformulation analysis that allowed a POSA to identify and address issues before substantial time was wasted. (Tr. 74:1-16, Tr. 98:16-99:14; SOF 133-34; *see also* DTX 91 at 91 ("Initial investigation begins through knowledge of the drug's chemical structure which allows the preformulation scientist to anticipate the possible degradation reactions.").)

Plaintiffs' reliance on the statement from Connors that "kinetically, [] there is sufficient energy barrier to many [oxidation] reactions . . . that not all molecules are subject to measurable rates of spontaneous oxidation or autooxidation" is misplaced. (Pl. Br. at 12.) This statement from JTX 22 does not demonstrate that "theoretical possibilities do not correlate with pharmaceutical realities," as Plaintiffs contend. (*Id.*) Rather, this quote stands for the unremarkable (and uncontested) proposition that "not all molecules" degrade by oxidative degradation. Dr. Schöneich, however, did not testify that all molecules are subject to oxidative degradation. Rather, he testified that a POSA would understand from an analysis of rivastigmine's structure (and not by testing) that it is particularly susceptible to oxidation due to the presence of a weak carbon-hydrogen bond. (SOF 142, 145, 158-60.) And Dr. Klibanov

provides no testimony that kinetic barrier issues are present with rivastigmine to otherwise counter that reasonable expectation.

C. Susceptibility to Oxidation Would Have Been Predictable to a POSA

A POSA in 1998 would have known that a drug molecule's susceptibility to oxidative degradation was predictable through the application of textbook chemical knowledge. (SOF 150; SOF Response 364-65.) Plaintiffs' attempts to impute "unpredictability" from notions of "complexity" fail because they only address the reaction mechanism of oxidation and not the susceptibility of the molecule itself to undergo the reaction. All of the art relied on by Plaintiffs explicitly relates to the *mechanisms* of oxidation and not to the susceptibility of a drug to oxidation. (SOF 151-53; SOF Response 356.) Moreover, none of the citations relied on by Plaintiffs state that oxidation reactions are "unpredictable" as Plaintiffs contend. (Pl. Br. 168 at 13.) Dr. Schöneich explained in unrebutted testimony that susceptibility to oxidation would have been predictable to a POSA and is independent from the mechanisms of oxidation reactions, which are complex due to the reactive nature of the free radicals involved in the initiation, propagation, and termination steps. Indeed, Dr. Schöneich cautioned against confusing the two concepts. (Tr. 78:6-21; SOF 151-52; SOF Response 356.) Plaintiffs' attempts to cast oxidation reactions as some sort of nascent field of chemistry is of course contradicted by the prior art's textbook teachings on the subject. (SOF 103, 133, 135-150.)

Plaintiffs' statement that the oxidation of drugs cannot be predicted is belied by testimony from their own expert. Dr. Klibanov agreed with the statement from *Modern Pharmaceutics* that:

through the application of functional group chemistry, it is possible to anticipate the potential mode(s) of degradation *that drug molecules will likely undergo*.

(PTX 153 at 181, emphasis added; Tr. 528:21-529:8.) Plaintiffs' tellingly omit the emphasized

portion of the above text when quoting *Modern Pharmaceutics*. (Pl. Br. 168 at 14.) Moreover, Dr. Klibanov relies on a table in the same textbook providing “some common functional groups” that the POSA would reasonably expect, if present in a molecule, to be subject to oxidation. (Tr. 524:3-19; PTX 153 at 183.) The predictive value of chemical structure analysis to the POSA is evidenced by such textbooks instructing the artisan to consider a molecule’s structural features to anticipate likely modes of degradation including oxidative degradation. (SOF Response 360-61; SOF 106, 133.)

While it is true that the cited table from *Modern Pharmaceutics* does not recite functional groups present in rivastigmine (PTX 153 at 183), the table illustrates that a POSA would make reasonable predictions that a molecule is susceptible to oxidation based on the presence of certain structural features like those listed in the table. The table, however, is titled “*some* functional groups” (PTX 153 at 183, emphasis added) and would be recognized by a POSA, as Dr. Klibanov confirmed, not to be an exhaustive list. (Tr. 524:13-525:7.) Other prior art confirms that functional groups in rivastigmine identified by Dr. Schöneich would have been understood by a POSA to be “especially susceptible to oxidation.” (DTX 32 at 693, “Benzylic . . . and tertiary positions are especially susceptible to oxidation”; SOF Response 361.)

Dr. Klibanov’s “real world examples” of commercial formulations without an antioxidant are admittedly meaningless when used to support Plaintiffs’ proposition that examination of chemical structure lacks predictive value. He confirmed that one cannot draw any conclusions regarding the drug’s susceptibility to oxidation by the lack of an antioxidant because a POSA could take other known steps to prevent oxidation.⁴ (Tr. 551:9-553:6; SOF Response 397, 401,

⁴ Additionally uninformative is Plaintiffs’ reliance on commercial formulations involving a drug not having all three of the structural features that Dr. Schöneich testified render rivastigmine particularly susceptible to oxidative degradation. (Pl. Br. at 16-17; SOF 171.)

481.) Dr. Schöneich agreed. (Tr. 91:8-92:2.)

Dr. Klibanov's testimony that a POSA would just assume that all drugs are stable "in the absence of any indication of instability" is unsupported and strips the POSA of the analytical skills a chemist would have based on the prior art. A POSA would not have blindly assumed a drug is stable until told otherwise, but, consistent with the prior art, would have investigated the stability of a drug through examination of its structure during preformulation development. (SOF 106, 111, 133.) "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

D. The Known Susceptibility of Nicotine to Oxidative Degradation Would Have Informed the POSA's Expectation About Rivastigmine

The relevant structural similarities between nicotine and rivastigmine, and nicotine's known susceptibility to oxidative degradation, would have reinforced the POSA's expectation that rivastigmine is particularly susceptible to oxidation. It is undisputed that nicotine was known to undergo oxidative degradation under pharmaceutically relevant conditions including in transdermal formulations. (SOF 162, 164, 398.) Dr. Klibanov testified that "under some pharmaceutically relevant conditions, nicotine was known to undergo oxidative degradation" and that the commercial product Habitrol utilized an airtight pouch to prevent oxidation of nicotine. (Tr. 452:1-5, 563:3-11.) Dr. Klibanov also admitted that the three structural features identified by Dr. Schöneich as causing rivastigmine to be susceptible to oxidation (*i.e.*, a tertiary carbon-hydrogen bond that is immediately adjacent to both an aromatic ring and a tertiary amine) are all present in nicotine (Tr. 539:15-541:23). Plaintiffs, while pointing out nominal and irrelevant differences between the two molecules, provide no reason why these distinctions would cause a POSA to conclude differently about rivastigmine.

IV. THE PRIOR ART DOES NOT TEACH THAT RIVASTIGMINE IS OXIDATIVELY STABLE

The prior art does not teach that rivastigmine (or its racemate, RA₇) is oxidatively stable. Plaintiffs only bases for their mistaken assertion that “the art as a whole teaches that rivastigmine is stable and does not require an antioxidant” (Pl. Br. at 3) are that (i) rivastigmine (and its racemate RA₇) were reported to have “greater chemical stability than physostigmine;” and (ii) prior art that did not address oxidative stability or state that an antioxidant is required. (Pl. Br. at 3-11.) Both bases fail to support Plaintiffs’ arguments.

The prior art comparisons between rivastigmine and physostigmine would not have indicated to a POSA that rivastigmine was *oxidatively* stable. The prior art comparisons do not refer to “chemical stability generally” as Plaintiffs argue, but rather, the prior art comparing the stability of rivastigmine to physostigmine addressed the known susceptibility of physostigmine to hydrolysis and rivastigmine’s resistance to hydrolysis. (SOF 156; SOF Response 256, 258-59, 291.)

Even if the prior art comparisons between rivastigmine and physostigmine relate to chemical stability generally, the comparison cannot portray the stability of rivastigmine (or RA₇) in a favorable light as Plaintiffs contend (Pl. Br. at 3-5, SOF 283) because the POSA would have known that physostigmine was a “chemically unstable” compound. (JTX 17 at 1:30-37, further stating that physostigmine has “a relatively short half-life (20-40 mins).”) Dr. Klibanov testified that monomethyl carbamates like physostigmine “tend to be unstable in a solution . . . and they *hydrolyze readily* at physiological pH” and that physostigmine was known to be a “particularly labile compound.” (Tr. 379:16-380:5, 424:6-425:23, emphasis added.) For these reasons, the prior art comparisons asserting that rivastigmine is more stable than physostigmine are inherently uninformative because it only establishes that rivastigmine is more stable than a particularly

problematic compound.

Plaintiffs' individual criticisms of GB '040, the '807 Patent, and Elmalem as not reciting that rivastigmine requires an antioxidant, even if true, do not control the analysis of obviousness. Plaintiffs' reference-by-reference analysis stating what is missing individually from each reference is not relevant to the question of obviousness, because it applies the standard for anticipation. *See e.g., Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1363 (Fed. Cir. 2005) (the district court erred in its obviousness analysis when it required the claims to be indistinguishable from the prior art).

Moreover, Plaintiffs' criticism of GB '040, the '807 Patent, and Elmalem as not suggesting oxidative instability attempts to rigidly apply the teaching, suggestion, motivation test, a practice forbidden by *KSR*. Motivation to add an antioxidant to a rivastigmine formulation need not be explicit in the prior art. *KSR*, 550 U.S. 398, 419. Motivation can come from the knowledge and common sense possessed by the ordinarily skilled artisan. *Id.* at 402-3. Here it is undisputed that a POSA would have knowledge of chemistry, which would include knowledge of bond-strengths and structural features that cause certain bonds to be particularly weak and therefore susceptible to oxidation. (SOF 2, 143, 150.) Therefore, even if GB '040, the '807 Patent, and Elmalem do not expressly disclose rivastigmine's oxidative behavior or provide motivation to add an antioxidant to rivastigmine formulation, the POSA's knowledge of chemistry and formulation principles from other prior art provides the expectation of rivastigmine's susceptibility to oxidative degradation. (SOF 106, 142-147, 150, 157-60.)

V. A POSA WOULD HAVE USED ANTIOXIDANTS AND THE PRIOR ART DID NOT TEACH AWAY FROM OR DISCOURAGE THEIR USE

Contrary to Plaintiffs' assertions, a POSA would have used antioxidants with a reasonable expectation of success, and the prior art as a whole did not discourage their use.

Plaintiffs do not dispute that oxidation was known in the art to be a prime cause of instability (SOF 120), or that antioxidants were a known solution to oxidative degradation. (SOF 111, 120, 183-85.) And Plaintiffs do not argue that the prior art “taught away” from antioxidant use with rivastigmine. There is no credible evidence that a POSA would have refrained from employing an antioxidant and would have harbored anything other than a reasonable expectation of success in employing one with rivastigmine. (SOF 85, 95-98, 183-85, 200; SOF Response 423.)

A POSA would have had good reason to add an antioxidant to stabilize a drug formulation because even minor amounts of drug degradation could result in the formation of toxic byproducts. (SOF Response 438.) Antioxidants were understood to prevent this potentially harmful degradation. (SOF 120.) Consistent with the prior art, it was therefore reasonable to ensure that a pharmaceutical composition was stable through use of an antioxidant. (SOF Response 438; PTX 153 at 179.)

It was known that numerous antioxidants were safe and non-toxic. (SOF 82-101; SOF Response 427-28.) Plaintiffs do not dispute that the prior art taught that specific antioxidants, such as tocopherol and citric acid,⁵ were safe and non-toxic. (SOF Response 436-38.) Dr. Klibanov admitted that a POSA would not have had toxicity or safety concerns as to ascorbic acid (vitamin C) or tocopherol (vitamin E), both of which are recited in claim 16. (Tr. at 512:18-516:5.)

Antioxidants were one of a small, finite group of known solutions to the problem of preventing or mitigating oxidative degradation for pharmaceutical active agents in a composition, (SOF 105; SOF Response 252, 280, 363, 420, 427-28, 439), including in transdermal

⁵ To the extent that Plaintiffs argue that citric acid is not an antioxidant (SOF Response 100), Plaintiffs’ argument directly contradicts the argument made in the *Novartis v. Par* litigation. *Novartis v. Par*, C.A. No. 11-1077 at D.I. 404, Plaintiffs’ Opening Post-Trial Brief Concerning Infringement at 19-21 (May 23, 2014).

formulations. (SOF 74-79, 203, 205, 207, 218.) Other means to prevent oxidation, such as removal of oxygen or the use of air-tight packaging, were understood to be sometimes difficult to employ successfully in practice. (SOF 74, 119.) The EMEA Guidelines, when viewed in total, suggests that antioxidant use should be justified, not, as Plaintiffs suggest, that they are a last resort after other possible solutions have been discounted. (SOF Response 424-26.) Dr. Klibanov never ties any alleged concerns about antioxidant use, in general, to rivastigmine in particular.

The prior art would have disclosed to a POSA that various antioxidants were compatible with rivastigmine. Dr. Kydonieus testified that the amount of BHA and citric acid disclosed in Example 2 of GB 040 was sufficient for a POSA to conclude that these antioxidants were compatible with rivastigmine. (SOF 32.) Dr. Kydonieus further testified that a POSA would have understood that Professor Weinstock's research group, which invented RA₇, disclosed sodium metabisulfite as a preferred antioxidant in the '807 patent, a patent which also discloses experimental data for RA₇ and a small group of other RA-series compounds. (SOF 56-57, 60, 207.) Professor Weinstock's group later, in Elmalem, unambiguously added this same antioxidant to a solution with RA₇ "to prevent oxidation." (SOF Response 245; SOF 37-38.) Further, the Handbook (JTX 8), which discloses incompatibility information for each antioxidant listed in claim 16, does not indicate any incompatibility towards amine compounds like rivastigmine. (SOF Response 419-20, 438.) A POSA would have readily found an antioxidant that worked for a particular rivastigmine formulation using well-known methods. (SOF 134; SOF Response 438.) Plaintiffs do not dispute that a POSA would have expected a good probability of success for finding an antioxidant that worked in a particular formulation. (SOF Response 438.) And Dr. Klibanov admitted that a POSA would only need one antioxidant to

work in order to obtain a working formulation.⁶ (SOF Response 438.) In short, a POSA would have maintained more than a reasonable expectation that an antioxidant compatible with rivastigmine could be identified.

Sasaki would have reinforced a POSA's expectation that antioxidants provided a viable solution to rivastigmine's susceptibility to oxidative degradation. Plaintiffs do not contest that Sasaki is a prior-art publication (SOF Response 71, 241), so attempts to disparage it as non-peer-reviewed or "unexamined" are irrelevant; Sasaki teaches all that it discloses and all that it would have suggested to a POSA. *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Although Plaintiffs also attempt to discredit the teaching of Sasaki by relying on examples of commercial formulations having no "reported" antioxidant, Dr. Klibanov conceded that such examples are not probative of any drug's susceptibility to oxidative degradation. (Tr. 551:23-552:16; SOF Response 397, 401, 481.) Also, although Plaintiffs rely on a claim that Sasaki discloses "just two" amine compounds, Dr. Kydonieus testified that Sasaki provides three additional examples of amine compounds that Plaintiffs ignore.⁷ (SOF 80; SOF Response 456-57.) Plaintiffs further identify no technical error in Sasaki's disclosure.

Dr. Kydonieus' testimony was consistent with the disclosure of Sasaki, contrary to Plaintiffs' implication otherwise. (Pl. Br. at 25.) When asked whether a tertiary amine compound would be susceptible to oxidative degradation, Dr. Kydonieus testified that he would "leave that question to the organic chemist." (Tr. 282:11-17.) Dr. Schöneich had already

⁶ Plaintiffs do not dispute that use of only one of the antioxidants recited in claim 16 need be obvious for the claim to be invalid. (Noven Brief at 17.)

⁷ Plaintiffs' argument that a POSA could not "extrapolate" from two Sasaki examples is in stark contrast to Plaintiffs' position in the *Novartis v. Par* litigation that a POSA *could* extrapolate from two examples of antioxidants given in the '031 patent to determine what other agents were "antioxidants." *Novartis v. Par*, C.A. 11-cv-1077 at D.I. 409, Plaintiffs' Answering Post-Trial Brief Concerning Validity at 8 (June 13, 2014).

answered this question in the affirmative. (Tr. 78:22-79:8.) Dr. Kydonieus also testified that oxidative degradation is “formulation dependent,” meaning that whether oxidation occurred to any appreciable extent would depend on the specifics of the formulation, but he also testified that the amine compounds disclosed by Sasaki are similar to rivastigmine, and thus a POSA would have understood that rivastigmine, like the amine compounds of Sasaki, is susceptible to degradation when combined with an acrylic adhesive (as was done in Example 2 of Enz). (Tr. 160:21-161:16, 164:1-165:5, 198:23-199:18, 282:24-283:11; SOF 80, 191.)

Also contrary to Plaintiffs’ suggestion, Ebert would have motivated a POSA to add an antioxidant to rivastigmine. Plaintiffs claim there is “no reason why” a POSA would select Ebert, but Dr. Schöneich and Kydonieus explained the reason is the similarity in structure between nicotine and rivastigmine. (SOF Response 470.) Plaintiffs rely on three nicotine patches without “reported” antioxidants, but again, such information is not probative of susceptibility to oxidative degradation (Tr. 553:1-6), and Plaintiffs ignore the fact that one of the three nicotine patches, Habitrol, included airtight packaging to prevent oxidation of nicotine. (SOF 164.) And contrary to Plaintiffs’ claims, Ebert is not limited to a certain method of manufacturing, or only to the drug nicotine—its teachings explicitly apply to other drugs. (SOF Response 463, 471, 472.) Ebert states that “it will be apparent to one skilled in the art that any other liquid drug contained in an active gel which can be transdermally or transmucosally delivered may be substituted in place of nicotine.” (SOF Response 463, 472.) And GB 040, for example, discloses the preparation of an active ingredient in a gel. (SOF Response 467.)

VI. CONCLUSION

For the foregoing reasons, claims 7 and 16 of the ’031 patent are invalid as obvious and for obviousness-type double patenting.

Respectfully submitted,

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